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SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/665,221	ARDIES, C. MURRAY	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/04,8/04p*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 28 October 2002, which claims benefit of the US provisional application 60/421,679 filed 28 October 2002. The preliminary amendment filed 3 March 2004 has been entered. Claims 1-23 were originally filed. Claims 1 and 12 were amended in the 3 March preliminary amendment. Claims 1-23 are pending.

Election/Restrictions

Applicant's election without traverse of the following species: i. MAPK pathways of claims 2 and 13; ii. reporter-gene assays of claims 4 and 15; and iii. increased cellular content of any gene product associated with the stress-response pathways in the reply filed on 18 September 2006 is acknowledged.

The nonelected embodiments set forth in the claims are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the 18 September reply.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The instant claims are directed to a method of screening agents to determine if such agents are useful for producing the health-benefits of exercise including the prevention and treatment of disorders selected from the group consisting of cachexia and other wasting disorders, cancer, atherosclerosis, heart disease, autoimmune disease, chronic inflammatory disease, alcoholic hepatitis, non-alcoholic hepatitis, rheumatoid arthritis, osteoarthritis, type II diabetes, insulin insensitivity, Parkinson's disease, Alzheimer's disease, and any other condition caused or mediated by chronic oxygen radical damage or by chronic chemical toxicities. Thus, the claims are directed to a method having the stated purpose of identifying agents that are useful for the prevention and treatment of a widely divergent genus of conditions.

The claimed invention comprises two process steps: treating cells of a living organism with a putative agent; and measuring transient activation of a stress-response pathway. Thus, the claims cover the method practiced with any cell of any organism (i.e., any cell of any plant or animal, be it a fungus, insect or mammal), wherein transient activation of any element of any stress response pathway is measured.

As the claims explicitly state that the outcome obtained by the method is the determination that an agent is useful for producing any of the widely divergent health benefits of exercise recited in the claims, the enabling disclosure must clearly and concisely teach the skilled artisan how to practice the claimed method such that an agent useful as recited is identified. Furthermore, as the enabling specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation[1], the disclosure must teach the skilled artisan how to practice the method using any cell of a living organism wherein any element of any stress response pathway is measured.

Amount of direction provided by the inventor and existence of working examples: With regard to working examples, the disclosure does not teach a method wherein an agent capable of preventing or treating any of the conditions recited in the claims is identified. Instead, the specification teaches that when rats were forced to run on a rodent treadmill for 60 minutes, the cJun protein transiently translocated to the nucleus in lung tissue. (See especially the paragraph bridging pp. 22-23.) In paragraph 0058, the specification teaches:

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[1] "Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' *Vaeck*, 947 F.2d at 495, 20 USPQ2d at 1444; Wands, 858 F.2d at 736-37, 8 USPQ2d at 1404; In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification)." *In re Wright* (CAFC) 27 USPQ2d 1510 at 1513.

> Any treatment which enhances the endogenous activation of any of these signal transduction or gene pathways will enhance endogenous activity of antioxidant and phase II enzymes, enhance insulin sensitivity, and increase rates of protein synthesis in skeletal muscle. Acute exercise activates these pathways through transient increases in cellular content of reactive oxygen species (H202) and calcium. These same pathways also are activated by transient increases in diacylglycerol or phosphatidylinositol metabolites. Based on these observations, any treatment which activates these same pathways also will result in these same benefits.

This conclusion is "based, in part, on the discovery that the risk-reduction and treatment benefits of exercise are due to a transient activation of signaling molecules or gene products common to the insulin signaling pathways, growth hormone, MAPK, SAPK and NFκB and possibly HIF pathways." (Paragraph 0024.) The specification teaches that repeated physical activity correlates with reduced risk for developing a variety of conditions including heart disease, cancer and diabetes. (See especially the discussion in paragraphs 0029-0031.)

The specification teaches that exercise enhances insulin sensitivity in skeletal muscle through a process that involves translocation of the GLUT4 protein to the cell membrane and enhanced expression of GLUT4 through a complex process involving a variety of signaling molecules and both insulin dependent and insulin independent pathways. (Paragraph 0035-0036.) The specification also teaches that activation of MAPK pathways is important in insulin and growth factor signaling. (See especially paragraphs 0040-0044.) The specification teaches that exercise enhances production of reactive oxygen species (ROS) and that ROS are involved as secondary messengers in the activation of PKC by signaling pathways which transduce signals from the cell nucleus to the membrane. (See especially paragraph 0046.) The specification teaches the interactive effects of physical exercise, insulin, and growth hormone on activation of the SAPK and MAPK pathways. (See especially paragraph 0048 and Figure 4.) The specification

teaches that exercise induces production of ROS, that ROS induce upregulation of antioxidant processes and that induction of antioxidant capacity can have beneficial effects in decreasing tumor growth. (See especially the discussion in paragraphs 0050-0053.) The specification teaches, the apparent paradox of an exercise-associated increase in ROS production being beneficial might be explained by the duration and intensity of the increase and that a transient and intermittent increase in ROS production due to physical exercise may be sufficient to activate various transcription enhancers to a sufficient degree in order to obtain beneficial (protective) outcomes without suffering the damaging effects of chronically enhanced ROS production.

On the whole, the disclosure appears to assert that, because exercise has many beneficial effects, because exercise results in production of ROS, because upregulation of antioxidant proteins has some benefit in slowing tumor cell growth, and because MAPK pathways are activated by therapeutic molecules such as growth hormone or insulin, the disclosure that exercise induces translocation of cJun to the nucleus in rat lung indicates that any agent capable of inducing transient activation of any stress-response pathway is useful for producing any or all of the health-benefits of exercise.

State of the prior art and level of predictability in the art: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there

is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. The physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fischer*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC §112, first paragraph requires that: the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The question of predictability in the instant case has to do with whether the skilled artisan would be able to extrapolate the disclosed translocation of cJun to the nucleus during exercise and the knowledge available in the art regarding stress-response pathway signaling such that the skilled artisan could practice the claimed method to determine if an agent is useful for producing health-benefits of exercise as broadly as is claimed.

The claimed method proposes to use the activation of any element of any stress-response pathway as a biomarker or surrogate endpoint for efficacy in the prevention or treatment of any of a host of disparate conditions. The art recognizes that before a putative biomarker can be used as a surrogate endpoint it must be validated as such. Wagner (2002) *Dis. Markers* 18:41-46 acknowledges in the Abstract, "Putative biomarkers are typically identified because of a relationship to known or hypothetical steps in a pathophysiologic cascade. Biomarker discovery

can also be effected by expression profiling experiment using a variety of array technologies and related methods." However, Wagner cautions, "A rational basis for recommending the use of a putative biomarker does not guarantee the utility of the biomarker or its qualification as a surrogate endpoint" (paragraph bridging the left and right columns on page 43) and "Biomarkers require validation in most circumstances" (paragraph bridging pages 43-44).

Frank *et al.* (2003) *Nature Rev.* 2:566-580 concurs, stating, "The standard concepts of test-re-test reliability and validity apply with equal force to clinical biomarkers as they do in any assay system" and, "The work required to establish the reliability and validity of a new biomarker should not be underestimated in general, and in particular needs of planning for each combination of clinical indication and mechanism of action" (paragraph bridging the left and right columns on page 568). Feng *et al.* (2004) *Pharmacogenomics* 5:709-719 teaches, "The development and validation of clinically useful biomarkers from high-dimensional genomic and proteomic information pose great research challenges. Present bottle necks include: that few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation...A molecular profiling approach, although promising, has a high chance of yielding biased results and overfitted models" (Abstract).

Viewed as a whole, the art clearly teaches that the utility of a putative biomarker as a surrogate endpoint for any disease state is unpredictable and must be validated.

In a post-filing publication (Ardies (2002) *Nutrition and Cancer* 42:143-157; made of record on the IDS filed 22 July 2004), Applicant discusses the finding that exercise induces cJun translocation disclosed in the instant Application and states:

> On the basis of these preliminary results, the possibility exists that a transient exercise/stress-mediated activation of the MAPK and/or JNK-MAPK pathway

> through enhanced Ca^{2+} and ROS is responsible for the enhanced activity of antioxidant enzymes and the phase II enzymes previously observed []. Because skeletal muscle is far more metabolically active than lung during exercise, on eight expect that the degree of an exercise-induced activation of AP-1 in muscle would be greater than in lung. As with the other proposed hypotheses, this remains to be thoroughly tested.

Thus, Applicant characterizes the results as preliminary and states that assertion that MAPK and/or JNK-MAPK is responsible for enhanced activity of antioxidant enzymes and phase II enzymes is a hypothesis that remains to be thoroughly tested.

With regard to the scope of the claims, the art teaches that stress-response pathways are extremely complex. Schaeffer et al. (1999) *Mol. Cell. Biol.* 19:2435-2444, teaches that there are a variety of pathways involving multiple signaling molecules leading to distinct outcomes depending upon the stimulus. (See especially Figure 1 and the caption thereto and the section entitled "Enzyme-Substrate Interactions".) Schaeffer et al. also teaches that understanding the roles and consequences of MAPK activation is particularly challenging in metazoan cells because each cell is simultaneously exposed to multiple extracellular signals and the response involves integration of the inputs. (See especially the first full paragraph in the right column on page 2435 and the section entitled "Specificity by Cross Talk and Signal Integration".) Thus, the meaning of activation of any given stress-response pathway in any given cell under any given set of circumstances is highly unpredictable.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to practice the claimed invention such that the outcome recited in the claim could be obtained without having to engage in undue experimentation to further develop the method.

The claims broadly encompass a method having the stated purpose of identifying agents that are useful for the prevention and treatment of a widely divergent genus of conditions wherein the claims cover the method practiced with any cell of any organism (i.e., any cell of any plant or animal, be it a fungus, insect or mammal), wherein transient activation of any element of any stress response pathway is measured. The basis for the claims is the recognized beneficial effects of exercise, the disclosure that exercise induces translocation of cJun to the nucleus in rat lung and various consequences of stress-response pathway activation in cells.

However, the art recognizes that stress-response signaling is extraordinarily complex and that the utility of a putative biomarker as a surrogate endpoint for any disease state is unpredictable and must be validated. Furthermore, in a post-filing publication, Applicant characterizes the findings disclosed in the instant application as preliminary and states that assertion that MAPK and/or JNK-MAPK is responsible for enhanced activity of antioxidant enzymes and phase II enzymes is a hypothesis that remains to be thoroughly tested. When the record is viewed as a whole it is clear that the usefulness of any given stress-response pathway signaling molecule in any given cell as a biomarker or surrogate endpoint for prophylactic or therapeutic efficacy in the prevention or treatment of any given condition is unpredictable and must be experimentally established on a case by case basis. Although the disclosure teaches that some therapeutic molecules activate MAPK pathways, the instant application fails to establish that activation of any given component of any stress-response pathway in any cell is a valid biomarker for prophylactic or therapeutic effect in any of the conditions recited in the claims. It is again noted that stress-response pathways are extraordinarily complex and activation of such pathways are commonly associated with pathological states such as cancer. Thus, in the instant

case, the disclosure of the claimed invention as a method of identifying agents useful in the prevention or treatment of any given condition amounts to no more than the germ of an idea in a highly unpredictable art.

"It must be remembered...that '[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure.' *Genentech*, 108 F.3d at 1366 (quoting *Brenner v. Manson*, 383 U.S. 519, 536 [148 USPQ 689] (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion')). Thus, while the need for some experimentation is by no means necessarily fatal, 'reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.' Id." *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 at 1436 (W.D.N.Y. 2003).

Given no more that what is provided in the instant application and the relevant art, the skilled artisan would not know how to practice the claimed invention (i.e., which cell to use, which signaling molecule to measure, etc.) such that an agent useful in the prevention or treatment of any given disease (e.g., Alzheimer's disease) is identified. Therefore, the skilled artisan would have to validate the activation of any given signaling molecule in any given cell as a marker for therapeutic or prophylactic efficacy in the treatment of any given condition. Given the unpredictable nature of the invention and the expansive scope of the claims, the amount of experimentation would clearly be undue. Therefore, the disclosure fails to adequately enable the claims and the claims are properly rejected under 35 U.S.C.§112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in reciting, "said pathways" in line 2. Claim 1, from which claim 3 depends, and claim 12, from which claim 14 depends, are directed to "measuring transient activation of a stress-response pathway". It is unclear whether the use of the plural "pathways" in claim 3 is intended to limit the claim to measuring transient activation of two or more pathways or whether measurement of a single stress-response pathway is within the scope of the claims. Amending the claim to recite "said stress-response pathway" would be remedial. It is noted that because the office considers the singular as encompassing both the singular and plural of a limitation, unless otherwise specified, the use of the singular would not be construed as limiting the claim to measuring activation of only a single pathway.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 8, 9, 11-16, 18, 19 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Valjent et al. (July 2001) *Eur. J. Neurosci.* 14:342-352.

Independent claim 1 is directed to a method of screening comprising treating cells of a living organism with a putative agent and measuring transient activation of a stress-response pathway. Likewise, independent claim 12 is directed to a method comprising treating living organisms with a putative agent and measuring transient activation of a stress-response pathway. The claims further recite, "wherein said transient activation indicates said putative agent is useful for prevention or treatment of [the disorders recited in the preamble]." However, the instant disclosure provides no basis for distinguishing a transient activation of a stress-response pathway that indicates an agent is useful for prevention or treatment of any particular disorder from a transient activation of a stress-response pathway that does not indicate an agent is useful for preventing or treating a disorder. Therefore, unless Applicant can establish that the method disclosed in the prior art would not indicate that an agent is useful for prevention or treatment of one of the conditions recited in the preamble, the property recited in the "wherein" clause is construed as an inherent property of the transient activation measured by the prior art method.

Valjent et al. teaches a method comprising treating cells of a living organism with Δ9-tetrahydrocannabinol (THC) and measuring transient activation of a stress-response pathway. Specifically, Valjent et al. administers THC to mice and assays for an increase in the presence of activated ERK using an antibody that specifically recognizes the active form of ERK2. (See especially the "Materials and methods section" at pp. 343-344, the section entitled "*Kinetics of ERK phosphorylation induced by THC in the dorsal striatum and NA*", and Figure 1 (especially

panel C).) The method of Valjent et al. comprises each of the elements of the method recited in the instant claims 1 and 12.

Furthermore, the limitation of the dependent claims can also be found in the teachings of Valjent et al. Valjent et al. teaches transient activation of the MAPK pathway according to the limitations of claims 2 and 13 and teaches transient activation of a signaling molecule with in the MAPK pathway according to the limitations of claims 3 and 14. The transient activation indicates, absent evidence to the contrary, that the agent is a source of an agent for treatment of a disorder according to the limitations of claim 5. The transient activation determined in the method of Valjent et al. is approximately 30-40 minutes in duration, which meets the limitations of claims 6 and 16, the transient activation is produced by modifying the dosing regimen (i.e., administering the THC to animals that had not previously received THC) according to the limitations of claims 8 and 18, and the cells of the organism are mammalian cells according to the limitations of claims 9 and 19.

Valjent et al. further teaches that the transient activation of the MAPK pathway by THC results in increased expression of *zif268*. (See especially the paragraph bridging pp. 347-348, the paragraph bridging pp. 348-349, Figure 4 and the caption thereto.) The *zif268* expression measured in the method of Valjent et al. is therefore a viable reporter for transient activation of the stress-response pathway and reads on the method of claims 4 and 15, wherein the measurement of transient activation is done using "any reporter-gene assay[] to determine gene activation" and the method of claims 11 and 23, wherein the transient activation is increased cellular content of a gene product associated with the stress response pathway.

The method of Valjent et al. comprises each of the elements of the method claimed in the instant application. Therefore, the claims are properly rejected under 35 USC §102(b) as anticipated by Valjent et al.

Claims 1-9, 11-19 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Valjent et al. (July 2000) *J. Neurosci.* 20:8701-8709 (hereinafter, Valjent et al. 2000).

The limitations of the claims are construed as described above.

Valjent et al. (2000) teaches a method comprising treating cells of a living organism with cocaine and measuring transient activation of a stress-response pathway. Specifically, Valjent et al. (2000) administers cocaine to mice and assays for an increase in the presence of activated ERK using an antibody that specifically recognizes the active form of ERK2. (See especially the "Materials and methods section" at p. 8702, the section entitled "**Acute cocaine treatment induced ERK activation throughout the striatum**", Figure 1 and the caption thereto.) It is particularly noted that Valjent et al. (2000) states, "One hour after cocaine injection, P-ERK immunostaining returned to basal levels (data not shown)." (P. 8702, col. 2, ¶6.) The method of Valjent et al. (2000) comprises each of the elements of the method recited in the instant claims 1 and 12.

Furthermore, the limitation of the dependent claims can also be found in the teachings of Valjent et al. (2000). Valjent et al. (2000) teaches transient activation of the MAPK pathway according to the limitations of claims 2 and 13 and teaches transient activation of a signaling molecule with in the MAPK pathway according to the limitations of claims 3 and 14. The transient activation indicates, absent evidence to the contrary, that the agent is a source of an

agent for treatment of a disorder according to the limitations of claim 5. The transient activation determined in the method of Valjent et al. (2000) is between 1 minute and 60 minutes in duration, which meets the limitations of claims 6 and 16, the transient activation is produced by modifying the dosing regimen (i.e., administering the cocaine to animals that had not previously received cocaine) according to the limitations of claims 8 and 18, and the cells of the organism are mammalian cells according to the limitations of claims 9 and 19.

Valjent et al. (2000) further teaches that the transient activation of the MAPK pathway by cocaine results in increased expression of c-fos. (See especially the paragraph bridging the left and right columns on p. 8705, Figure 5 and the caption thereto.) The c-fos expression measured in the method of Valjent et al. (2000) is therefore a viable reporter for transient activation of the stress-response pathway and reads on the method of claims 4 and 15, wherein the measurement of transient activation is done using "any reporter-gene assay[] to determine gene activation" and the method of claims 11 and 23, wherein the transient activation is increased cellular content of a gene product associated with the stress response pathway.

Finally, Valjent et al. (2000) teaches the method wherein the mice are treated with cocaine once daily for 6 days. (see especially p. 8702, col. 2, ¶6.) Once daily for 6 days meets the limitations of not more than three times in one day and not less than once each day for three non-consecutive days according to claim 7 and meets the limitations of not more than three times in one day and not less than once each day for three consecutive days according to the limitations of claim 17.

The method of Valjent et al. (2000) comprises each of the elements of the method claimed in the instant application. Therefore, the claims are properly rejected under 35 USC §102(b) as anticipated by Valjent et al. (2000).

Claims 1-3, 5, 6, 8-14, 16, 18-20 and 23 are rejected under 35 U.S.C. 102(a) as being anticipated by van den Blink et al. (2001) *Mol. Med.* 7:755-760.

The limitations of the claims are construed as described above.

Van den Blink et al. teaches a method comprising treating cells of a living organism with lipopolysaccharide (LPS) and measuring transient activation of a stress-response pathway. Specifically, van den Blink et al. administers LPS to humans and assays for an increase in the presence of phosphorylated p44/42 MAPK, phosphorylated JNK and phosphorylated p38 MAPK using an antibodies that specifically recognizes the phosphorylated form of the proteins. (See especially the "Materials and methods section" at p. 756, the section entitled "*Endotoxemia Induces Transient Phosphorylation of p38 MAPK and p42/44 MAPK*", Figures 4 and 5 and the caption thereto.) The method of Van den Blink et al. comprises each of the elements of the method recited in the instant claims 1 and 12.

Furthermore, the limitation of the dependent claims can also be found in the teachings of Van den Blink et al. Van den Blink et al. teaches transient activation of the MAPK pathway according to the limitations of claims 2 and 13 (see especially Figures 4 and 5) and teaches transient activation of a signaling molecule with in the MAPK pathway according to the limitations of claims 3 and 14. The transient activation indicates, absent evidence to the contrary, that the agent is a source of an agent for treatment of a disorder according to the limitations of

claim 5. The transient activation determined in the method of Van den Blink et al. is between approximately 4 to 8 hours in duration, which meets the limitations of claims 6 and 16, the transient activation is produced by modifying the dosing regimen (i.e., administering the LPS to subjects that had not previously received LPS) according to the limitations of claims 8 and 18, and the cells of the organism are human cells according to the limitations of claims 9, 10, 19 and 20.

Van den Blink et al. further teaches increased cellular content of the phosphorylated form of p38 MAPK (Figure 4A) and increased cellular content of the phosphorylated form of p42/44 MAPK (Figure 5A). As the phosphorylated forms of p38 MAPK and p42/44 MAPK are "gene products associated with the stress-response pathways" the teachings of van den Blink et al. meet the method of claims 11 and 23, wherein the transient activation is increased cellular content of a gene product associated with the stress response pathway.

The method of Van den Blink et al. comprises each of the elements of the method claimed in the instant application. Therefore, the claims are properly rejected under 35 USC §102(b) as anticipated by Van den Blink et al.

Claims 1-3, 5, 6, 8-14, 16 and 18- 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Victor et al. (1993) *J. Biol. Chem.* 268:18994-18999.

The limitations of the claims are construed as described above.

Victor et al. teaches a method comprising treating cells of a living organism with tumor necrosis factor-α (TNF-α) and measuring transient activation of a stress-response pathway. Specifically, Victor et al. administers TNF-α to cultured human fibroblasts and assays for an

increase in the presence of phosphorylated p44/42 MAPK by determining a PAGE mobility shift and phosphorylation of the MAPK protein. (See especially the "Materials and methods section" at p. 18995, the sections entitled "*MAPK Activation in FS-4 Cells Treated with TNF*" and "*Increased Tyrosine Phosphorylation of MAPK in TNF-treated cells*", Figures 1 and 2 and the captions thereto.) The method of Victor et al. comprises each of the elements of the method recited in the instant claims 1 and 12.

Furthermore, the limitation of the dependent claims can also be found in the teachings of Victor et al. Victor et al. teaches transient activation of the MAPK pathway according to the limitations of claims 2 and 13 (see especially Figure 1B) and teaches transient activation of a signaling molecule within the MAPK pathway according to the limitations of claims 3 and 14. The transient activation indicates, absent evidence to the contrary, that the agent is a source of an agent for treatment of a disorder according to the limitations of claim 5. The transient activation determined in the method of Victor et al. is greater than 1 minute and less than 60 minutes in duration, which meets the limitations of claims 6 and 16 (se especially Figure 1B), the transient activation is produced by modifying the dosing regimen (i.e., administering the TNF-α to subjects that had not previously received LPS) according to the limitations of claims 8 and 18, and the cells of the organism are human cells according to the limitations of claims 9, 10, 19 and 20.

Victor et al. further teaches increased cellular content of the phosphorylated form of MAPK (Figures 1 and 2). As the phosphorylated forms of MAPK is a "gene product associated with the stress-response pathways" the teachings of Victor et al. meet the method of claims 11

and 23, wherein the transient activation is increased cellular content of a gene product associated with the stress response pathway.

Finally, claim 21 limits the method to treating cultured tissues from a mammal and claim 22 limits the cultured tissues of claim 21 to being from human. Stedman's Medical Dictionary (27th Edition online) defines a tissue as "A collection of similar cells and the intercellular substances surrounding them." In view of this definition, the cultures of human fibroblasts of Victor et al., which would comprise a collection of similar human cells and intercellular substances surrounding them, meet the limitations of a tissue from a human according to the broadest reasonable interpretation of the claims. Therefore, the teachings of Victor et al. anticipate the limitations of claims 21 and 22.

The method of Victor et al. comprises each of the elements of the method claimed in the instant application. Therefore, the claims are properly rejected under 35 USC §102(b) as anticipated by Victor et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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